sa surface et greffe de cellules souches neurales. L'originalité repose sur l'utilisation de cellules souches neurales adultes naturellement présentes dans le cerveau, qui peuvent être multipliées en vitro, et le fait que le support ou prothèse portant les cellules souches sera dessiné et fabriqué par lithographie. À travers le contrôle très précis de la topographie du polymère constituant la prothèse, nous allons induire l'adhésion et la différentiation des cellules souches, et nous serons capables de guider les neurones régénérés le long de directions spécifiques. Une fois équipée avec des cellules fonctionnelles, la prothèse devient une bioprothèse qui peut être implantée par chirurgie. Cette technologie peut être utilisée pour diverses pathologies du SNC. Dans ce projet, nous nous focalisons sur la régénération après accident vasculaire cérébral.
Nous optimisons le dessin de la prothèse en termes de matériel biocompatible, micro/nano-structuration (taille, forme et profondeur des motifs topographiques), coating chimiques et fonctionnalisation moléculaire. Nous avons aussi évalué le bénéfice potentiel ou la toxicité des nanotubes de carbone (NTC) double-paroi sur la viabilité cellulaire, l'adhésion et la différentiation. Ce travail se décline en trois parties : la fabrication de la bioprothèse, sa caractérisation in vitro par histologie et électrophysiologie, et sa validation fonctionnelle chez le rongeur par imagerie in vivo, histologie et évaluation comportementale. Le cœur du projet est de remplacer le faisceau corticospinal, guider la croissance axonale jusqu'à la capsule interne, et induire une récupération motrice chez le rat. L'immunogénicité de la bioprothèse, la réponse inflammatoire de l'hôte et la biodégradation des produits après l'implantation seront étudiés.
Ce projet est hautement interdisciplinaire, implique aussi bien des neurologues, des neurochirurgiens impliqués dans l'implantation cérébrale et la biopsie de cellules souches adultes humaines, des chercheurs en neuroimagerie, des biologistes impliqués dans la culture cellulaire et la caractérisation (Inserm UMR 825 ; Cerco), ainsi que des chimistes experts en synthèse et fonctionnalisation de nanomatériaux (CIRIMAT, LSPCMIB), des physiciens impliqués dans les nanotechnologies et la nanofabrication (LAAS, ITAV).

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## *English version*

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### Monoamines drugs in post-stroke motor recovery

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*Keywords:* Stroke; Recovery; Fluoxetine; Brain plasticity; Motor function; Mono-aminergic drugs
Until now, rTPA thrombolysis within the first hours of the stroke is recognized as the only validated treatment able to improve the spontaneous Å and most of the time incomplete Å recovery of neurological functions after stroke. However, we have learnt from research over the last decade, in part based on the considerable improvement of neuroimaging techniques, that spontaneous recovery of neurological functions was associated with a large intracerebral reorganization of the damaged human brain. The question of whether lesioned-brain plasticity can be modulated by external factors like pharmacological agents is now addressed with the aim of improving recovery and reducing the final disability of patients. We review in this talk, the preclinical and clinical arguments for a direct action of monoamines in promoting recovery after stroke in humans.

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### Cortical non-invasive stimulations and post-stroke motor recovery

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Recovery of function after stroke occurs largely on the basis of a maintained capacity of the adult brain for plastic changes and this human brain capacity has been demonstrated by means of functional imagery and electrophysiological studies (suractivation of lesioned cortex, involvement of compensatory areas at distance from the infarct, compensatory changes in somatosensory or motor somatotopies). Various concepts of how to enhance beneficial plasticity and in turn improve recovery of function are emerging based on the concept of functional interhemispheric balance between the two motor cortices. Beside conventional rehabilitation interventions and more recent neuropharmacological approaches, non-invasive brain stimulation (NIBS) have been recently proposed as add-on methods to promote the recovery of motor function after stroke.
Several methods can be used based either on the application of transcranial magnetic stimulation (repetitive mode: rTMS, TBS), via a coil, or small electric current in the order of 1 to 2 mA via larges electrodes placed on the scalp, (transcranial direct current stimulation tDCS). Depending on the different electrophysiological parameters of stimulation used, NIBS can induce a transient modulation of the excitability of the stimulated motor cortex (facilitation or inhibition) via a probable LTP-LTD-like mechanism. Several small studies have shown feasible and positive treatment effects for most of these strategies and their potential clinical interest to help at restoring the disruption of interhemispheric imbalance after stroke. Results of these studies are encouraging but many questions remain unresolved: what are the optimal stimulation parameters, what is the best NIBS intervention? Which cortex lesioned or intact must be stimulated? What is the best window of intervention (acute, subacute or chronic recovery phase?), is there a special subgroup of stroke patients who can have the strongest benefit from these interventions? If so, how can this subgroup be identified before the treatment? Finaly is it possible to boost NIBS treatment effect by motor practice of the paretic hand or by additional neuropharmacological intervention? There is clearly a need for large-scale controlled multicenters trials to answer these questions before proposing their use routinely in the management of post-stroke patients.

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### Non-invasive brain stimulations and post-stroke motor recovery

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*Keywords:* Stem cells; Stroke; Nanotechnology; Animal models
The main objective of Innov-in-Stroke project is to develop a generic technology for repairing Central Nervous System (CNS) damages through an implantable prosthesis that combines Micro/Nano-engineering of its surface and graft of neural stem cells. The originality relies on the use of human adult neural stem cells which are naturally present in the brain and can be expanded in vitro and the fact that the material hosting the stem cells will be designed and fabricated by lithography. Through the very precise control of the topography of the polymer constituting the prosthesis, we will induce stem cell adhesion and differentiation and we will be able to guide the regenerated neurons along specific directions. Once equipped with functional stem cells, the lithographically designed prosthesis becomes a bioprosthesis which can be implanted through surgery. The developed technology can be used for various repairing applications in the CNS. In this project, we will mainly focus on brain regeneration after stroke.
We optimize the design of the prosthesis in terms of biocompatible support material, micro/nanopatterning (size, shape and depth of topographical features), specific chemical coating and molecular functionalization. We also investigated the possible benefit or toxicity of Double walled CNT (DWCNT) for stem cells viability, adhesion and differentiation. The project is divided in

three main work packages: the bioprosthesis manufacturing, the bioprosthesis characterization in vitro by histology and electrophysiology, and the functional validation of the bioprosthesis in rodents by in vivo imaging, histology and behavioural assessment. The core of the project will be to replace the corticospinal tract, guide axonal growth to the internal capsule, and induce a functional motor recovery in rats. The immunogenicity of the bioprosthesis, the inflammatory response from the host to the prosthesis and to the biodegradation products released after implant will be also investigated.

This project is highly interdisciplinary, involving on the one hand neurologists, neurosurgeons involved in brain implantation and human adult neural stem cells biopsy, researcher in neuroimaging, biologists involved in cell culture and characterization (Inserm UMR 825; Cerco) and on the other hand chemists involved in nanomaterial (CNTs) synthesis and functionalization (CIRIMAT, LPCMIB), physicists involved in nanotechnology and nanofabrication (LAAS, ITAV).

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